WE CLAIM:

1. A method for producing and identifying an active doublestranded RNA (dsRNA) which attenuates a desired gene expression in a cell, said method comprising:

(a) producing a plurality of cDNA, wherein each cDNA comprises at least a portion of a gene that is expressed in a cell;

(b) producing a candidate dsRNA from at least one of the cDNA;

(c) introducing the candidate dsRNA into a reference cell; and

(d) identifying an active dsRNA by determining whether the candidate dsRNA modulates a desired candidate gene expression in the reference cell.

2. The method of Claim 1 further comprising producing the identified active dsRNA from a corresponding cDNA of step (a).

3. The method of Claim 1, wherein said step of identifying the active dsRNA comprises:

(A) selecting a candidate gene, wherein the candidate gene is a gene that is expressed in a test cell and/or a control cell, and/or is expressed at a detectably different level with respect to the test cell and the control cell, and the test cell and control cell differ with respect to a cellular characteristic; and

(B) identifying whether the candidate dsRNA is an active dsRNA by determining whether down-regulation of expression of the candidate gene in a reference cell has a functional effect in the reference cell, wherein the determining step comprises:

(i) introducing the candidate dsRNA which is substantially identical to at least a part of the candidate gene into the reference cell; and

(ii) detecting an alteration in a cellular activity or a cellular state in the reference cell, alteration indicating that the candidate gene plays a functional role in the reference cell and is an active dsRNA.

4. The method of Claim 1, wherein said step of producing a plurality of cDNA comprises:

(i) isolating at least one mRNA from the cell, and

(ii) producing a double-stranded cDNA from the isolated mRNA by reverse transcription.

5. The method of Claim 4, wherein step of producing a plurality of cDNA further comprises producing cDNAs of a similar length by digesting cDNA of said step (ii) with a restriction enzyme.

6. The method of Claim 5, wherein said step (b) of producing the candidate dsRNA comprises:

(i) producing a plasmid or PCR fragment from the cDNA, and

(ii) producing the candidate dsRNA from the plasmid or PCR fragment.

7. The method of Claim 6, wherein the plurality of cDNA comprises at least a portion of substantially all genes that are actively expressed in the cell.

8. The method of Claim 6, wherein the desired affect of the candidate dsRNA on the reference cell is a result of the candidate dsRNA attenuating expression of a candidate gene in the reference cell.

9. The method of Claim 8, wherein the candidate dsRNA has complete sequence identity with the candidate gene over at least 100 nucleotides.

10. The method of Claim 9, wherein the candidate dsRNA has complete sequence identity with the candidate gene over at least 500 nucleotides.

11. The method of Claim 1, wherein the candidate dsRNA is at least 100 nucleotides in length.

12. The method of Claim 11, wherein the candidate dsRNA is at least 500 nucleotides in length.

13. The method of Claim 12, wherein the candidate dsRNA is between 500 and 1100 nucleotides in length.

14. A method for identifying and validating the effect of an active double-stranded RNA (dsRNA) which attenuates a desired gene expression in a cell, said method comprising:

(a) producing a candidate dsRNA which comprises at least a portion of a candidate gene that is expressed in a control cell;

(b) introducing the candidate dsRNA into a reference cell; and

(c) identifying whether the candidate dsRNA is an active dsRNA by detecting an alteration in a cellular activity or a cellular state in the reference cell, alteration indicating that the candidate gene plays a functional role in the reference cell and is an active dsRNA.

15. The method of Claim 14, wherein said step of producing the candidate dsRNA comprises:

(i) producing a cDNA from a mRNA of the control cell such that the cDNA comprises at least a portion of the gene that is expressed in the control cell; and

(ii) producing the candidate dsRNA from at least one of the cDNA of said step (i).

16. The method of Claim 14, wherein the candidate gene is a gene that is expressed in a test cell and/or the control cell, and/or is expressed at a detectably different level with respect to the test cell and the control cell, and the test cell and control cell differ with respect to a cellular characteristic.

17. A method for correlating genes and gene function, said method comprising:

(a) producing a plurality of candidate dsRNAs from a plurality of cDNAs of a control cell such that each candidate dsRNA comprises at least a portion of a gene that is expressed in the control cell;

(b) introducing each of the candidate dsRNA into a plurality of separate reference cell each having a gene expression similar to the control cell in step (a); and

(c) identifying which candidate dsRNA is an active dsRNA by detecting an alteration in a cellular activity or a cellular state in the reference cell, desired alteration indicating that the gene corresponding to the candidate dsRNA plays a functional role in the reference cell.

18. The method of Claim 17, wherein the plurality of cDNAs is produced from a plurality of mRNAs which are produced by the control cell.

19. The method of Claim 18, wherein said step of producing a plurality of cDNA comprises:

(i) isolating at least one mRNA from the cell;

(ii) producing a double-stranded cDNA from the isolated mRNA by reverse transcription;

(iii) producing cDNAs of a similar length by digesting cDNA of said step (ii) with a restriction enzyme; and

(iv) producing a plasmid or PCR fragment from the cDNA of said step (iii).

20. The method of Claim 19, wherein the candidate dsRNA is produced by transcribing the plasmid cDNA or PCR fragment of said step (iv).

21. The method of Claim 19, wherein the plurality of cDNA comprises at least a portion of substantially all genes that are actively expressed in the cell.

22. The method of Claim 19, wherein the restriction enzyme is selected from the group consisting of Dpn1 and Rsa1.

23. The method of Claim 17, wherein said step of producing the plurality of candidate dsRNAs comprises:

(A) selecting a candidate gene, wherein the candidate gene is a gene that is expressed in a test cell and/or a control cell, and/or is expressed at a detectably different level with respect to the test cell and the control cell, and the test cell and control cell differ with respect to a cellular characteristic; and

(B) producing the plurality of candidate dsRNAs, wherein each candidate dsRNA is substantially identical to at least a part of the candidate gene.

24 The method of claim 23, wherein the candidate gene is selected from a normalized library prepared from cells of the same type as the test cell or the control cell and is present in low abundance in the normalized library.

25. The method of claim 23, wherein the candidate gene is a differentially expressed gene selected from a subtracted library that is enriched for genes that are differentially expressed with respect to the test cell and the control cell.

26. The method of claim 25, wherein the subtracted library is also normalized and the candidate gene is one of the genes that is both present in low abundance and differentially expressed in the subtracted and normalized library.

27. The method of claim 23, wherein said step of selecting the candidate gene comprises:

(i) preparing

(A) a tester-normalized cDNA library which is a normalized library prepared from test cells;

(B) a driver-normalized cDNA library which is a normalized library prepared from control cells;

(C) a tester-subtracted cDNA library which is enriched in one or more genes that are up-regulated with respect to the test cell and the control cell, and

(D) a driver-subtracted cDNA library which is enriched in one or more genes that are down-regulated with respect to the test cell and the control cell; and

(ii) identifying one or more clones from the normalized libraries and/or the subtracted libraries,

wherein the candidate gene is one of the clones identified.

28. The method of Claim 27, wherein said step of identifying one or more clones from the normalized libraries comprises:

(A) contacting clones from the tester-normalized cDNA library with labeled probes derived from mRNA from test cells and contacting clones from the driver-normalized cDNA library with labeled probes derived from mRNA from control cells under conditions whereby probes specifically hybridize with complementary clones to form a first set of hybridization complexes; and

(B) detecting at least one hybridization complex from the first set of hybridization complexes to identify a clone from one of the normalized libraries which is present in low abundance.

29. The method of Claim 27, wherein said step of identifying one or more clones from the subtracted libraries comprises:

(A) contacting clones from the tester-subtracted cDNA library and contacting clones from the driver-subtracted cDNA library with a population of labeled probes under conditions whereby probes from the population of probes specifically hybridize with complementary clones to form a second set of hybridization complexes, and wherein the population of labeled probes is derived from mRNA from test cells and control cells; and

(B) detecting at least one hybridization complex from the second set of hybridization complexes to identify a clone from one of the subtracted libraries which is differentially expressed above a threshold level with respect to the subtracted libraries.

30. The method of claim 23, wherein the cellular characteristic is cell health, the test cell is a diseased cell and the control cell is a healthy cell, and the candidate gene is potentially correlated with a disease.

31. The method of claim 30, wherein the test cell is obtained from a mammal that has had a stroke or is at risk for stroke.

32. The method of claim 30, wherein the test cell is obtained from a mammal that has a neurological disease or develop phenotypes mimicing human neurological diseases.

33. The method of claim 23, wherein the cellular characteristic is stage of development and the test cell and the control cell are at different stages of development, and the candidate gene is potentially correlated with mediating the change between the different stages of development.

34. The method of claim 23, wherein the cellular characteristic is cellular differentiation and the candidate gene is potentially correlated with controlling cellular differentiation.

35. The method of claim 23, wherein the candidate gene is an endogenous gene of the reference cell.

36. The method of claim 23, wherein the candidate gene is present in the reference cell as an extrachromosomal gene.

37. The method of claim 17, wherein the reference cell is part of a cell culture.

38. The method of claim 17, wherein the reference cell is part of a tissue.

39. The method of claim 17, wherein the reference cell is part of an organism.

40. The method of claim 17, wherein the reference cell is part of an embryo.

41. The method of claim 17, wherein the reference cell is a mammalian cell.

42. The method of claim 17, wherein the reference cell is a neural or glial cell.

43. The method of claim 42, wherein the reference cell is a neuroblastoma cell.

44. The method of claim 43, wherein the reference cell is useful as a model system for investigating neurological disease in humans.

45. The method of claim 44, wherein the reference cell has increased sensitivity to N-methyl-D-aspartate, β-amyloid, peroxide, oxygen-glucoe deprivation, or combinations thereof.

46. The method of claim 45, wherein the detecting step comprises detecting a decrease in cellular sensitivity to N-methyl-D-aspartate, β-amyloid, peroxide, oxygen-glucoc deprivation, or combinations thereof.

47. The method of claim 17, wherein the detecting step comprises detecting modulation of ligand binding to a protein.

48. The method of claim 17, wherein the reference cell is a part of an organism and the detecting step comprises detecting a change in phenotype.

49. The method of claim 17, wherein the determining step comprises determining whether interference with expression of the candidate gene in the reference cell is correlated with alteration of a cellular activity or cellular state.

50. The method of claim 49, wherein interference is achieved by introducing a double-stranded RNA into the reference cell that can specifically hybridize to the candidate gene.

51. The method of claim 17, wherein the determining step comprises determining whether the protein encoded by the candidate gene binds to another protein to form a complex that can be coimmunoprecipitated.

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